REMARKS

Upon entry of the foregoing amendment, claims 1-68 are pending in this application, with claims 1, 13, 25, 37, 51 and 67 being the independent claims. Support for the amendments to claims 1, 7, 13, 19,25, 30, 37, 42, 51, 56 and 67 are found, *inter alia,* on page 17, lines 9-end to page 18, lines 22; page 13, lines 12-15; page 18, lines 3-5, and, elsewhere throughout the specification. Support for amendments to dependent claims is found throughout the specification and in original claims 1-68. Amendments were made to correct improper antecedent basis and to more clearly claim the invention. Support for the insertion of SEQ ID No. 1 is found, *inter alia,* in the Lanza *et al.* publication, cited on page 19, lines 30-31, incorporated by reference into this application (page 1, lines 26-29). Support for the Abstract as added is found in application WO 99/53032. It is believed no new matter has been introduced by these changes and entry thereof is respectfully submitted.

The Office Action dated August 2, 2001 (Paper No. 5) has been carefully reviewed. In view of the amendments above and the following remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections and the timely allowance of the pending claims.

Priority

At page 2 of the Office Action, the Office notes that the instant application appears to claim subject matter disclosed in prior copending applications PCT/US99/08285, filed April 15, 1999 and Provisional Patent Application No. 60/115,516, filed April 15, 1998. The Office further states a reference to the prior applications must be inserted in the first sentence if applicant intends to rely on the filing date of the prior application under 35 U.S.C. § 119(e) or 120.

In response thereto, the specification has been amended (See, above) to include a statement regarding claims to priority in the first sentence. In addition, the specification has also been amended to include the current status of the cited related nonprovisional applications as it is known. In view of the amendments, it is believed the issues have been resolved.

Rejection under 35 U.S.C. § 101

At page 2 of the Office Action, the Office rejects claims 1-24 under 35 U.S.C § 101 because the claims read on non-human mammals comprising naturally occurring mutations of the GP IIIa gene. The rejection is respectfully traversed.

Without acquiescing to the position of the Office, claims 1, 13, 25, 37, 51 and 67 are newly amended to recite, *inter alia*, the word "transgenic." It is believed that the claim as now amended distinguishes non-human mammals comprising naturally occurring mutations of the GP IIIa gene from the non-human mammals of the invention. In view of the amendments above, it is believed the rejection of claims 1-24 has been overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

At page 12 of the Office Action, the Office rejects claims 1-68 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is respectfully traversed.

The Office rejects independent claim 1, and claims 2-12 dependent therefrom, because claim 1 recites the phrase "the gen" in line 2 of claim 1. However, careful review of original claim 1 does not find the cited error. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects independent claim 13, and claims 14-24 dependent therefrom, as vague and confusing for recitation of the term "DNA" which can refer to either genomic or mitochondrial DNA. The Office suggests the claim be rewritten to state "a transgene stably introduced into its genome." In response thereto, newly amended claim 13 now recites, *inter alia,* the phrase "its genome." Support for the amendment is found, *inter alia*, in Examples 4 and 5, pages 21-22, and elsewhere throughout the specification. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects independent claim 25, and claims 26 –36 dependent therefrom, because the term "regenerating" in part (b) of the claim is vague and confusing. In response thereto, newly amended claim 25 now recites "generating." Support for the amendment to claim 25 is found, *inter alia*, on page 15, lines 16-23 and elsewhere throughout the specification. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects independent claim 37, and claims 38-50 dependent therefrom, because the term "regenerating" in part (e) is vague and unclear. In response thereto, newly amended claim 37 now recites "generating." Support for the amendment to claim 37 is found, *inter alia*, on page 15, lines 16-23 and elsewhere throughout the specification. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects claims 27, 32, 39, 44, 53 and 58 as having insufficient antecedent basis for the phrase "the cytoplasmic tyrosine residues" in line 1 of the claims. However, claims 25, 27, 32, 39, 44, 53 and 58 as newly amended now recite "phosphorylatable cytoplasmic domain

tyrosine residues." Support for the amendment to the claims is found, *inter alia*, on page page 15, line 1. It is believed the amendment to claims 25, 27, 32, 39, 44, 53 and 58 to now recite "phosphorylatable cytoplasmic domain tyrosine residues" overcomes the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects claims 30, 42 and 56, and claims 31-34, dependent from claim 30, as having insufficient antecedent basis for the phrase "phosphorylatable cytoplasmic tyrosine residues" in line of the claims. However, claims 30, 42 and 56 as newly amended now recite the phrase "phosphorylatable cytoplasmic domain tyrosine residues." Support for the amendment to the claims is found, *inter alia*, on page 15, line 1. It is believed the amendment to claims 30, 42 and 56 to now recite "phosphorylatable cytoplasmic domain tyrosine residues" overcomes the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects claim 51, and claims 52-66 dependent therefrom, as lacking positive recitation of basic method steps. In response, newly amended claim 51 now comprises a method for determining mutant GP IIIa protein modulation on one or more biological responses, said method comprising treating wild-type and transgenic non-human mammals with an agent and comparing one or more biological responses between the non-transgenic and transgenic non-human mammal. Support for the amendment is found, *inter alia*, on page 15, lines 24-end to page 16, lines 1-17. It is believed the amendments to claim 51 overcome the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects claims 61-65, dependent from independent claim 51, for having insufficient antecedent basis for the phrase "the bleeding time," "the two mammal types," and, "the thrombotic responses." However, claim 51 has been amended (See, above) and claims 61-65 have been amended to more clearly claim the invention. It is believed the amendments overcome the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects claim 67 for having insufficient antecedent basis for the phrase "said administration." Claim 67, part (b), has been amended to include the phrase "administering said agent." It is believed the amendments overcome the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office rejects claim 68 for having insufficient antecedent basis for the phrase "the mammal" in line 1 of the claim. However, claim 68 has been amended to now recited the phrase "said transgenic, non-human mammal." It is believed the amendments overcome the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

At page 2 of the Office Action, the Office rejects claims 1-68 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, has possession of the claimed invention. The rejection is respectfully traversed.

The Office asserts the specification fails to describe any other species within the genus of mutant GP IIIa genes from any species, wherein at least one of the two cytoplasmic tyrosine residues encoded by the gene has been replaced with any other non-tyrosine residue, encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention. The Office further asserts the invention "as a whole" is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' effective filing date. According to the Office, the skilled artisan cannot envision all such mutant GP IIIa genes and therefore conception is not achieved until reduction to practice has occurred. The Office concludes that only the described mutant murine GP IIIa gene where at least one of the two

cytoplasmic tyrosine residues (747 and 759) has been replaced with a phenylalanine residue meets the written description requirements of 35 U.S.C. §112, first paragraph.

However, contrary to the position of the Office, the specification provides adequate written description of the claimed invention. The specification has been amended to include the entire amino acid sequence of the GP IIIA cytoplasmic domain. This sequence is set forth as SEQ ID No. 1 and clearly shows multiple tyrosine residues available for phosphorylation including residues 747 and 759. This sequence has been incorporated by reference to the Lanza document (See above). Thus specific written description is now provided for residues 747 and 759 and for cytoplasmic domain of GP IIIa. In light of the highly conserved nature of the gene, one of ordinary skill would find adequate guidance and written description to practice the invention across the full scope of the invenation as claimed. The Office has not established adequate reason why undue experimentation and/or additional description would be required.

Rejection under 35 U.S.C. § 112, first paragraph

At page 5 of the Office Action, the Office rejects claims 1-68 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is respectfully traversed.

The Office asserts that the specification fails to provide an enabling disclosure for the preparation of the exemplified transgenic mice exhibiting an appropriate phenotype. The Office further asserts that because the specification discloses no phenotype for the exemplified mice, undue experimentation would be required to make and/or use the invention.

However, contrary to the position of the Office, the phenotype is disclosed on page 18, lines 15-18, wherein it is disclosed that normal platelet aggregation is dependent on phosphorylation. The specification further states the transgenic mammals of the present invention will display non-normal platelet aggregation. In further support, presented herewith as Exhibit A is Applicants' publication entitled "Integrin cytoplasmic tyrosine motif is required for outside-in IIb 3signalling and platelet function," Law *et al.*, Nature 401: 808-811 (1999). The publication demonstrates (page 808, column 2, lines 4-7) that the mice are selectively impaired in outside-in IIb 3signalling, with defective aggregation and clot-retraction responses *in vitro,* and an *in vivo* bleeding defect which is characterized by a pronounced tendency to rebleed. Thus, the specification does disclose a phenotype. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office asserts that the mere capability to perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs of the types recited in the claims. The Office further asserts that while gene transfer techniques are well developed for a number of species, methods for achieving the desired levels of transgene expression in other species are less well established. The Office concludes that without evidence to the contrary, transgene expression is not predictable and varies according to host species and specific promoter/gene combinations.

However, contrary to the position of the Office, the claims do not claim any particular level of expression. Further, the interrelationship of GP IIIa protein phosphorylation with numerous cellular responses has been established (specification pages 2 and 3; specification page 4 to page 5, "Tyrosine Phosphorylation of the Cytoplasmic Domain of Integrin subunits"). It is asserted that GP IIIa expression, despite species variation, would result in a discernible phenotype. Reconsideration and withdrawal of the rejection is respectfully requested.

The Office asserts the specification fails to provide an enabling disclosure the preparation of any transgenic animals harboring any mutant GPIIIa gene because the guidance in the specification is not sufficient to teach one skilled in the art how to prepare the claimed transgenic animals exhibiting an appropriate phenotype. The Office further asserts that the specification does not provide guidance for the generation of any species of animal ES cells other than the mouse which can give rise to the germline tissue of a developing animal.

However, undue experimentation is not required. The specification discloses a phenotype for the claimed transgenic mice. One of ordinary skill would find adequate guidance and written description to practice the invention across the full scope of the invention. The Office has not met the burden of explaining why the invention is not enabled across the full scope of the invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned at his convenience.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. § 1.16 and § 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account

50-0310. This paragraph is intended to be a Constructive Petition for Extension of Time in accordance with 37 C.F.R § 1.136(a)(3).

Respectfully submitted

Morgan, Lewis & Bockius LLP

Dated: January 2, 2002

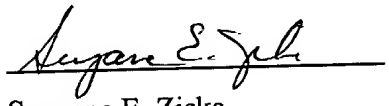
Morgan, Lewis & Bockius LLP

Customer No. **09629**

1800 M Street, N.W.

Washington, D.C. 20036

202-467-7000



Suzanne E. Ziska

Registration No. 43,371

MARKED UP VERSION OF THE CHANGES TO THE SPECIFICATION

SPECIFICATION

A paragraph at page 1, beginning at line 3 has been replaced with the following paragraph:

Cross Reference to Related Applications

This application is a National Stage Application of PCT International Application No. PCT/US99/08285, filed April 15, 1999, and claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 60/115,516, filed April 15, 1998, now abandoned, incorporated by reference herein in its entirety.

A paragraph at page 1, beginning line 26 has been replaced with the following paragraph:

This application is related to U.S. Patent Application No. 08/734,607, filed October 18, 1996; U.S. Provisional Application No. 60/031,665, filed November 21, 1996; U.S. Provisional Application No. 60/042,093, filed March 28, 1997; and, U.S. Patent Application No. 08/975,653, filed November 21, 1997. All of the publications and patent applications that are identified in this specification are hereby incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

A paragraph at page 19, lines 24-31 has been replaced with the following paragraph:

The sequence for the murine genomic DNA is not known and has not been published, however part of the amino acid sequence of mouse GP IIIa was available (Cietat et al. (1993) *Biochem et Biophys Res Comm.* 193: 771-778, and Dr Jean-Phillipe Rosa, *Unite INSERM* 348, Paris) and its similarity to human GP IIIa sequence suggested the genomic GP IIIa from humans and mice could be fairly similar. Therefore, several PCR primers were generated towards the mouse GP IIIa sequence in areas which, in the case of human GP IIIa (SEQ ID N0. 1), spanned the two exons known to encode the cytoplasmic domain of GP IIIa ie. exons M and N (Lanza, F. et al. (1990) *J. Biol. Chem.* 265: 18098-18103). These primers were then tested with total

A paragraph on page 20, starting at line 14 has been added:

--The amino acid sequence having SEQ ID N0. 1 is as follows:

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GPNICTTRGV SSCQQCLAVS PMCAWCSDEA LPLGSPRCDL KENLLKDNCA PESIEFPVSE     60
ARVLEDRPLS DKGSGDSSQV TQVSPQRIAL RLRPDDSKNF SIQVRQVEDY PVDIYYLMDL    120
SYSMKDDLWS IQNLGTKLAT QMRKLTSNLR IGFGAFVDKP VSPYMYISPP EALENPCYDM    180
KTTCLPMFGY KHVLTLTDQV TRFNEEVKKQ SVSRNRDAPE GGFDAIMQAT VCDEKIGWRN    240
DASHLLVFTT DAKTHIALDG RLAGIVQPND GQCHVGSDNH YSASTTMDYP SLGLMTEKLS    300
QKNINLIFAV TENVVNLYQN YSELIPGTTV GVLSMDSSNV LQLIVDAYGK IRSKVELEVR    360
DLPEELSLSF NATCLNNEVI PGLKSCMGLK IGDTVSFSIE AKVRGCPQEK EKSFTIKPVG    420
FKDSLIVQVT FDCDCACQAQ AEPNSHRCNN GNGTFECGVC RCGPGWLGSQ CECSEEDYRP    480
SQQDECSPRE GQPVCSQRGE CLCGQCVCHS SDFGKITGKY CECDDFSCVR YKGEMCSGHG    540
QCSCGDCLCD SDWTGYYCNC TTRTDTCMSS NGLLCSGRGK CECGSCVCIQ PGSYGDTCEK    600
CPTCPDACTF KKECVECKKF DRGALHDENT CNRYCRDEIE SVKELKDTGK DAVNCTYKNE    660
DDCVVRFQYY EDSSGKSILY VVEEPECPKG PDILVVLLSV MGAILLIGLA ALLIWKLLIT    720
IHDRKEFAKF EEERARAKWD TANNPLYKEA TSTFTNITYR GT                       762
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The claims have been amended as follows:

1. (Once Amended) 1.A transgenic non-human mammal comprising a transgene comprising a mutant GP IIIa gene wherein said mutant gene encodes a mutant GPIIIa protein, said mutant protein having one or more [wherein at least one of the two] phosphorylatable cytoplasmic domain tyrosine residues [of the gene has been] replaced with a non-tyrosine residue.

2. (Once Amended) The transgenic non-human mammal of claim 1 wherein [the] said non-tyrosine residue is phenylalanine.

3. (Once Amended) The transgenic non-human mammal of claim 1 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No 1.

4. (Once Amended) Platelets isolated from the blood plasma of [the] said transgenic non-human mammal of claim 1.

5. (Once Amended) The transgenic non-human mammal of claim 1 wherein [the] said transgenic non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

6. (Once Amended) The transgenic non-human mammal of claim 5 wherein [the] said non-human mammal is a mouse.

7. (Once Amended) The transgenic non-human mammal of claim 1 wherein [both] two phosphorylatable cytoplasmic domain tyrosine residues have been replaced with a non-tyrosine residue.

8. (Once Amended) The transgenic non-human mammal of claim 7 wherein [the] said non-tyrosine residues are phenylalanine.

9. (Once Amended) The transgenic non-human mammal of claim 7 wherein said phosphorylatable [the] cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No 1.

10. (Once Amended) Platelets isolated from [the] blood plasma of said transgenic [the] non-human mammal of claim 7

11. (Once Amended) The transgenic non-human mammal of claim 7 wherein [the] said transgenic non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

12. (Once Amended) The transgenic non-human mammal of claim 11 wherein [the] said transgenic non-human mammal is a mouse.

13. (Once Amended) A transgenic non-human mammal expressing a transgene [stably introduced] integrated into its genome [DNA], wherein [the] said transgene comprises DNA encoding mutant GP IIIa protein, wherein one or more phosphorylatable [at least one of the two] cytoplasmic domain tyrosine residues has been replaced with a non-tyrosine residue.

14. (Once Amended) The transgenic non-human mammal of claim 13 wherein [the] said non-tyrosine residue is phenylalanine.

15. (Once Amended) The transgenic non-human mammal of claim 13 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No. 1.

16. (Once Amended) Platelets isolated from [the] blood plasma of [the] said transgenic non-human mammal of claim 13.

17. (Once Amended) The transgenic non-human mammal of claim 13 wherein [the] said transgenic non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

18. (Once Amended) The transgenic non-human mammal of claim 17 wherein [the] said transgenic non-human mammal is a mouse.

19. (Once Amended) The transgenic non-human mammal of claim 13 wherein [both] two phosphorylatable cytoplasmic domain tyrosine residues have been replaced with a non-tyrosine residue.

20. (Once Amended) The transgenic non-human mammal of claim 19 wherein [the] said non-tyrosine [residues are] residue is phenylalanine.

21. (Once Amended) The transgenic non-human mammal of claim 19 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No. 1.

22. (Once Amended) Platelets isolated from [the] blood plasma of [the] said transgenic non-human mammal of claim 19.

23.(Once Amended) The transgenic non-human mammal of claim 19 wherein [the] said transgenic non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

24. (Once Amended) The transgenic non-human mammal of claim 23 wherein [the] said transgenic non-human mammal is a mouse.

25.(Once Amended) A method of preparing a transgenic [transformed] non-human mammal comprising a transgene comprising [with] a mutant GP IIIa gene, wherein said mutant gene encodes a mutant GP IIIa protein, said mutant protein having one or more [gene wherein at

least one of the two] cytoplasmic domain tyrosine residues [of the endogenous GP IIIa gene has been] replaced with a non-tyrosine residue [to prepare the mutant GP IIIa], said method comprising:

a) introducing into embryonic stem cells a nucleic acid molecule comprising said transgene comprising said mutant GP IIIa gene, wherein said mutant gene encodes [the] said mutant GP IIIa protein [gene];

b) [regenerating] generating a [transformed] transgenic non-human mammal from the cells [resulting from] of step a).

26. (Once Amended) The method of claim 25 wherein [the] said non-tyrosine residue is phenylalanine.

27.(Once Amended) The method of claim 25 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No. 1.

28. (Once Amended) The method of claim 25 wherein [the] said transgenic non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

29. (Once Amended) The method of claim 28 wherein [the] said transgenic non-human mammal is a mouse.

30. (Once Amended) The method of claim 25 wherein [both] two or more phosphorylatable cytoplasmic domain tyrosine residues have been replaced with a non-tyrosine residue.

31. (Once Amended) The method of claim 30 wherein [the] said non-tyrosine residues are phenylalanine.

32. (Once Amended) The method of claim 30 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No. 1.

33. (Once Amended) The method of claim 30 wherein [the] said transgenic non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

34. (Once Amended) The method of claim 33 wherein [the] said transgenic non-human mammal is a mouse.

35. (Once Amended) The method of claim 25 further comprising [breeding the transformed] mating said transgenic non-human mammal, followed by selecting [so as to produce] a non-human mammal [homozygotic] homozygous for [the] said mutant GP IIIa gene.

36. (Once Amended) The method of claim 35 wherein [the] said transgenic non-human mammal is a mouse.

37. (Once Amended) A method of preparing a [transformed] transgenic non-human mammal [with] comprising a transgene comprising a mutant GP IIIa gene encoding a mutant GP IIIa protein, [wherein] said mutant protein having one or more phosphorylatable [at least one of the two] cytoplasmic domain tyrosine residues [of the endogenous GP IIIa gene has been] replaced with a non-tyrosine residue [to prepare the mutant GP IIIa], said method comprising:

a) introducing into embryonic stem cells a nucleic acid molecule comprising a transgene comprising said mutant GP IIIa gene encoding [the] mutant GP IIIa [gene] protein and a selectable marker flanked by FRT sites, to produce one or more transformed embryonic stem cells;

(b) identifying and selecting said transformed cells;

c) removing [the] said selectable marker from said [the] transformed cells selected in step b) by transient transformation with FLP recombinase;

d) injecting [the] transformed cells from step c) into one or more blastocysts; and,

e) [regenerating] generating a [transformed] transgenic non-human mammal from [the] said blastocysts of step d), wherein [the] said transgenic [regenerated transformed] non-human mammal comprising said transgene comprising mutant GP IIIa gene is [chimeric] heterozygous for [the] said mutant GP IIIa gene.

38. (Once Amended) The method of claim 37 wherein [the] said non-tyrosine residue is phenylalanine.

39. (Once Amended) The method of claim 37 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No. 1.

40. (Once Amended) The method of claim 37 wherein [the] said transgenic non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

41. (Once Amended) The method of claim 37 wherein [the] said transgenic non-human mammal is a mouse.

42. (Once Amended) The method of claim 37 wherein [both] two phosphorylatable cytoplasmic domain tyrosine residues have been replaced with a non-tyrosine residue.

43. (Once Amended) The method of claim 37 wherein [the] said non-tyrosine residues are phenylalanine.

44. (Once Amended) The method of claim 37 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No. 1.

45. (Once Amended) The method of claim 43 wherein [the] said transgenic non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

46. (Once Amended) The method of claim 45 wherein [the] said transgenic non-human mammal is a mouse.

47. The method of claim 37 further comprising [breeding the] mating said transgenic [transformed] non-human mammal, followed by selecting [so as to produce] a transgenic non-human mammal [homozygotic] homozygous for [the] said mutant GP IIIa gene.

48. The method of claim 47 wherein [the] said non-human mammal is a mouse.

49. The method of claim 37 further comprising [the following steps]:

f) [breeding the chimeric non-human mammal with a wild-type non-human mammal to produce a non-human mammal heterozygotic for the mutant GP IIIa gene;]

[g)] [crossing] mating a [heterozygotic] heterozygous transgenic non-human mammal [produced in step (f)] with a second [heterozygotic] heterozygous transgenic non-human mammal [produced in step f)]; and,

h) selecting a transgenic non-human mammal [homozygotic] homozygous for the mutant GP IIIa gene from the resulting progeny.

50. The method of claim 49 wherein [the] said transgenic non-human mammal is a mouse.

51. A method for determining mutant GP IIIa protein modulation of one or more biological responses, said method comprising : treating transgenic and non-transgenic non-human mammals with one or more agents affecting said one or more biological responses; and, comparing [a characteristic] said one or more biological responses between a transgenic and a non-transgenic non-human mammal [two mammals] of the same species, wherein said non-transgenic non-human [one] mammal [has a] comprises wild-type GP IIIa genes and the [other] transgenic, non-human mammal [has a] comprises one or more mutant GP IIIa genes, wherein said mutant gene encodes a mutant GP IIIa protein, said mutant protein having at least one or more phosphorylatable [of the two] cytoplasmic domain tyrosine residues [of the wild-type GP IIIa gene has been] replaced with a non-tyrosine residue in the mutant GP IIIa gene.

52. (Once Amended) The method of claim 51 wherein [the] said non-tyrosine residue is phenylalanine.

53. (Once Amended) The method of claim 51 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID No. 1.

54. (Once Amended) The method of claim 51 wherein [the] said transgenic and non-transgenic non-human [mammal is] mammals are selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

55. (Once Amended) The method of claim 54 wherein [the] said non-human mammal is a mouse.

56. (Once Amended) The method of claim 51 wherein [both] two phosphorylatable cytoplasmic domain tyrosine residues have been replaced with a non-tyrosine residue.

57. (Once Amended) The method of claim 56 wherein [the] said non-tyrosine residues are phenylalanine.

58. (Once Amended) The method of claim 56 wherein [the] said phosphorylatable cytoplasmic domain tyrosine residues are tyrosine residues 747 and 759 of SEQ ID NO. 1.

59. (Once Amended) The method of claim 56 wherein [the] said transgenic and non-transgenic non-human [mammal is] mammals are selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

60. (Once Amended) The method of claim 59 wherein [the] said transgenic non-human mammal is a mouse.

61. (Once Amended) The method of claim 51 [further] wherein said biological response is [comprising comparing the] bleeding time [between the two mammal types].

62. (Once Amended) The method of claim 51 [further comprising] wherein said biological response is [comparing the] thrombotic response [responses between the two mammal types].

63. (Once Amended) The method of claim 51 [further comprising] wherein said biological response is [comparing] angiogenesis [between the two mammal types].

64. (Once Amended) The method of claim 51 [further comprising] wherein said biological response is [comparing] tumor metastasis [between the two mammal types].

65. (Once Amended) The method of claim 51 [further comprising] wherein said biological response is [comparing] inflammation [between the two mammal types].

66. (Once Amended) The method of claim 51 wherein [the] said mammal is a mouse.

67. (Once Amended) A method of determining the effect of an agent on a [characteristic] biological response of a transgenic, non-human mammal [that] wherein said biological response is modulated by GP IIIa phosphorylation [is attributable to the expression of the GP IIIa gene], said method comprising[;] :

a) administering said agent to [the] said transgenic non-human mammal of claim 1;

b) maintaining said transgenic, non-human mammal for a desired period of time after [said administration] administering said agent; and,

c) determining [whether] the effect of said agent on a biological response modulated by [characteristic of said mammal that is attributable to the expression of the] mutant GP IIIa [gene] phosphorylation in said transgenic, non-human mammal [has been affected by the administration of said agent].

68. (Once Amended) The method of claim 67 wherein [the] said transgenic, non-human mammal is a mouse.

A Sequence listing, pages 1-9, has been added to the specification.

An Abstract has been added to the specification.